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In This Issue

Influenza Vaccination: 1997-1998

Each year, infections due to the influenza virus result in substantial morbidity and mortality worldwide. Vaccination offers appreciable protection against the influenza virus for individuals and contributes to improved public health.

A new trivalent vaccine is now available for the 1997-1998 influenza season. The vaccine is recommended for patients with chronic medical disorders, children with asthma, residents of long-term care facilities, and the elderly. Health-care workers and household contacts of elderly and high-risk patients are also strongly encouraged to receive the vaccine.

Protection conferred by the influenza vaccine typically begins two weeks after vaccination and may last for six months or longer. Serum anti-bodies in some elderly patients can diminish more rapidly to non-protective levels. Because large outbreaks in the United States usually occur between December and early March, the optimal time to receive the vaccination is between October and November. However, administration of the vaccine is appropriate anytime from September to the end of the influenza season.

The vaccine formulation is changed annually because of the antigenic variability of the influenza virus. Antigens in the current vaccine are derived from *A/Johannesburg/82/96 (H1N1), A/Nanchang/933/95 (H3n2)and B/Harbin/07/94.*

Influenza vaccine is produced from inactivated virus grown in chicken eggs. Individuals who have experienced severe hypersensitivity reactions to eggs or egg products should not receive the vaccine. An intramuscular dose of 0.5 mL of the split-virus formulation can be administered (in the deltoid)to adults and children at least three years of age. Recipients of the vaccine may experience soreness at the site of injection, fever, and malaise that may persist for one or two days.

Questions about influenza or the vaccine should be directed to the Hospital Epidemiology Service at 6-2209 or the NIH Drug Information Service at 6-2407. For questions about the vaccination schedule, contact the Occupational Medical Service at 6-4411.

Troglitazone (Rezulin®): A Brief Review

Troglitazone is the first of a new class of oral medications (thiazolidinedione derivatives) for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It increases insulin sensitivity in skeletal muscle and adipose tissue and decreases hepatic gluconeogenesis. Troglitazone was approved by the FDA on January 29, 1997 for the treatment of NIDDM.

Description: Troglitazone (Rezulin®) is marketed by Parke-Davis and is available as 200 mg, 300 mg, and 400 mg tablets.

Indications: Troglitazone is indicated for concomitant use with insulin or a sulfonylurea to improve glycemic control in patients with NIDDM. Troglitazone may also be used as monotherapy in patients with NIDDM not adequately controlled on diet alone.

Pharmacology: Troglitazone lowers blood glucose levels by improving insulin sensitivity in target cells and inhibiting hepatic gluconeogenesis. Although the exact mechanism of action is not fully understood, troglitazone is thought to bind to peroxisome proliferator-activated receptor gamma (PPARγ) in the nucleus of hepatic muscle and adipose cells. PPARγ is involved in the transcription of certain genes that regulate glucose and lipid metabolism. Binding of troglitazone to PPARγ is thought to activate transcription and expression of certain genes that play a key role in proper carbohydrate and lipid metabolism. Troglitazone decreases hepatic glucose synthesis and triglyceride synthesis and

increases the uptake of glucose by skeletal muscle and adipose tissue. These actions occur in the presence of insulin. Troglitazone does not affect insulin secretion.

Pharmacokinetics: Troglitazone is rapidly absorbed following oral administration, with peak plasma concentrations occurring within 2-3 hours after oral administration. The presence of food increases the extent of troglitazone absorption by approximately 30% to 85%. Therefore, it is recommended that troglitazone be administered with a meal. In a study conducted in 21 healthy volunteers, the maximum plasma concentration (Cmax) and area-under-the-plasma-concentration time curve (AUC) of troglitazone increased in proportion to increasing dose. The Cmax ranged from 0.90 μg/mL to 2.82 μg/mL, and the AUC ranged from 7.4 μg.hr/mL to 22.1 μg.hr/mL with doses of 200 to 600 mg per day. Steady state plasma concentrations of troglitazone were obtained after 3-5 days of therapy, and the mean apparent volume of distribution (Vd) of troglitazone was reported to be 10.5 - 26.5 L/kg. Troglitazone is highly bound to serum albumin (>99%). It is extensively metabolized by the liver. Three troglitazone metabolites have been identified: a sulfate conjugate (Metabolite 1), a glucuronide conjugate (Metabolite 2) and a quinone metabolite (Metabolite 3). Troglitazone is primarily excreted in the feces (88%), and very small amounts have been detected in the urine. The mean plasma elimination half-life of troglitazone ranges from 16-34 hours. Human *in vivo* investigations have indicated that troglitazone may induce the cytochrome P450 3A4 enzyme pathway and could result in clinically significant drug interactions.

Selected Clinical Studies:

Troglitazone in combination with insulin therapy: Raskin et al studied 351 subjects with NIDDM who had failed to maintain adequate diabetic control (HbA_{1C} values ranging from 8.0% to 12.0%) with insulin doses > 30 units per day. Subjects were randomized into three treatment groups to receive 200 mg of troglitazone (n = 116), 400 mg of troglitazone (n =116), or placebo (n = 118) every morning. The primary outcome measures were the change from baseline in HbA_{1C}, fasting blood glucose, and insulin requirements. After 26 weeks of treatment, the adjusted mean changes from baseline in both troglitazone treatment groups were significantly greater ($p < 0.0001$) than those of the placebo group for all outcome measures.

Additional data on file from Parke-Davis indicate that 65% of subjects receiving troglitazone 600 mg, 48.3% of subjects receiving troglitazone 200 mg, and 21.1% of subjects in the placebo group, were able to reduce their daily insulin requirements by ≥ 12.5% during this 26-week trial. In addition, 4 subjects who were treated with 600 mg of troglitazone completely discontinued exogenous insulin therapy. The incidence of reported adverse effects was similar between both troglitazone treatment groups and the placebo group.

Gumbiner and colleagues conducted a similar multicenter, double-blind, placebo-controlled trial to evaluate the efficacy of troglitazone in obese patients with non-insulin-dependent diabetes who were not adequately controlled with insulin therapy. The primary treatment goal was to achieve a 50% reduction in total insulin requirements and a >15% decrease in fasting blood glucose values. A total of 222 obese subjects (mean BMI > 35 kg/m^2) with NIDDM, who were receiving an average of 72 units of insulin per day, were randomized to receive troglitazone 200 mg (n = 75), troglitazone 400 mg (n = 76), or placebo (n = 71) once daily. After 26 weeks of treatment, 27% of subjects in the troglitazone 400 mg group, 22% of subjects in the troglitazone 200 mg group, and 7% of the subjects in the placebo group reached the target treatment goal for both insulin dose reduction and fasting blood glucose values. This was statistically significant for both of the troglitazone treatment groups ($p < 0.05$). Parke-Davis (data on file) reports that subjects in the troglitazone 200 mg and 400 mg groups decreased their total insulin dosage by averages of 43% and 51%, respectively, and 15% of the subjects taking 400 mg of troglitazone were able to discontinue insulin therapy. The mean change in the number of daily insulin injections was also reported as -1.2, -1.4, and -2.0, for the placebo, troglitazone 200 mg, and troglitazone 400 mg groups, respectively.

Troglitazone in combination with a sulfonylurea: Troglitazone has also been evaluated in combination with a sulfonylurea agent. Ghazzi and colleagues evaluated the efficacy and safety of combination therapy in 541 patients with NIDDM who were not controlled adequately on maximum doses of an oral sulfonylurea. Patients were given 12 mg of Glynase® daily for 4 weeks. Subjects with fasting glucose values greater than 140 mg/dL at the end of this 4-week baseline period were randomized to receive one of seven blinded treatments. These treatment groups included Glynase® 12 mg, troglitazone 200 mg, troglitazone 400 mg, troglitazone 600 mg, Glynase® 12 mg and troglitazone 200 mg, Glynase® 12 mg and troglitazone 400 mg, and Glynase® 12 mg and troglitazone 600 mg daily. After one year of treatment, subjects receiving combination therapy with the sulfonylurea and troglitazone had the most significant decreases in HbA_{1c} and fasting glucose levels. Specifically, 6.3% of subjects receiving Glynase® alone reached HbA_{1c} values ≤ 7.9% ,while 30.8%, 31.6%, and 57.5% of subjects receiving Glynase® in combination with troglitazone 200 mg, 400 mg, and 600 mg doses, respectively achieved HbA_{1c} values ≤ 7.9%. The incidence of adverse events and withdrawal rates were similar between all treatment groups.

Iwamoto et al also studied the efficacy of troglitazone therapy in combination with sulfonylurea agents. Two-hundred ninety-one Japanese patients with NIDDM and poor glycemic control, despite treatment with glibenclamide [glyburide] or gliclazide, who had fasting plasma glucose levels higher than 8.3 mmole/L [149 mg/dL]were randomized to receive either troglitazone 200 mg (n = 122) or placebo (n = 126) twice daily for 12 weeks. At the end of the treatment period, there was a significant decrease in both fasting plasma glucose (10.8 ± 2 mmole/L[195mg/dL ± 36 mg/dL]vs 9.2 ± 2.5 mmole/L[165mg/dL ± 45 mg/dL]; $p<0.001$) and HbA_{1c} values (9.2 ± 1.4% vs 8.5 ± 1.5%; $p<0.001$) in the troglitazone treated group. These outcome measures were not altered in the placebo group. No serious adverse events were reported with this drug combination and glycemic control was significantly improved.

Troglitazone as Monotherapy for NIDDM: Iwamoto studied 262 subjects with NIDDM and poor glycemic control (fasting plasma glucose ≥ 150 mg/dL) who were previously

treated with diet therapy alone. Subjects were randomized to receive either placebo (n = 126) or 400 mg of troglitazone (n = 136) for 12 weeks. Fasting plasma glucose (-23.4 mg/dL) and HbA_{1c} values (-0.5%) were significantly decreased in the troglitazone treatment group and were unchanged in the placebo group. A statistically significant decrease in triglycerides was also reported in the troglitazone-treated group. This was only observed, however, in subjects who had high triglyceride values at baseline.

Information available in the FDA-approved product labeling reports unpublished data from a 6-month multicenter study conducted in subjects wtih NIDDM who were previously treated with diet or sulfonylureas to evaluate the efficacy of troglitazone monotherapy. A 2-week washout period was completed by all subjects prior to randomization. Subjects were randomized to receive either placebo or troglitazone 100 mg, 200 mg, 400 mg, or 600 mg once daily for 6 months. Hemoglobin A_{1c} and fasting glucose values were decreased in all of the troglitazone treatment groups and was statistically significant for the 600 mg treatment group, but only for those patients who were previously treated with diet. In patients who were previously treated with a sulfonylureas, troglitazone monotherapy did not result in an improvement above that of the patients' previous therapy. Troglitazone also reduced triglycerides and fasting free fatty acids and increased LDL cholesterol and HDL cholesterol. The cholesterol/HDL and LDL/Apo B ratios were unchanged in all troglitazone treatment groups.

Troglitazone for the treatment of glucose intolerance: Several small studies have evaluated the effects of troglitazone therapy in obese and insulin-resistant patients with impaired glucose tolerance. Nolan et al evaluated oral and IV glucose tolerance tests in 18 non-diabetic obese patients (9 with impaired glucose tolerance) who were randomized to receive either troglitazone 200 mg twice daily or placebo for 12 weeks. Subjects who received troglitazone had an increased calculated insulin-sensitivity index, a decreased glycemic response, and a decreased fasting insulin plasma concentration. There were no changes noted in the placebo group.

Forty-two Hispanic women with impaired glucose tolerance and a history of gestational diabetes mellitus were randomized to receive placebo, 200 mg, or 400 mg of troglitazone. After 12 weeks of treatment, the calculated insulin sensitivity increased 40% $\pm$ 22% for subjects receiving 200 mg of troglitazone and 88% $\pm$ 22% for subjects receiving 400 mg of troglitazone. Glucose tolerance improved only slightly in all groups. The lack of significant improvement in glucose tolerance was attributed to a beta-cell defect found in women with gestational diabetes.

Forty-six patients with impaired glucose intolerance, as defined by WHO criteria, were randomized to receive either 400 mg of troglitazone or placebo for 12 weeks. Glucose, insulin, and C-peptide responses following oral glucose tolerance tests were significantly reduced at both 6 and 12 weeks in the troglitazone treatment group, with 75% of the troglitazone-treated subjects having normal glucose tolerance tests at the end of 6 weeks and 80% having normal glucose tolerance tests at the end of 12 weeks of therapy.

Troglitazone has also been investigated in the treatment of other disorders which involve insulin resistance. For example, a three-month study conducted in 25 women with polycystic ovary syndrome treated with either 200 mg of troglitazone or 400 mg of troglitazone reported increased insulin sensitivity, and two women began to have ovulatory menses.

Adverse Effects: Troglitazone therapy was well tolerated during clinical trials, and the incidence of most reported adverse events related to troglitazone was similar to those reported by the placebo group. Adverse events reported in $\geq$ 5% of patients receiving troglitazone during clinical trials include headache, infection, pain, accidental injury, asthenia, dizziness, back pain, nausea, rhinitis, diarrhea, urinary tract infections, peripheral edema, and pharyngitis.

During clinical trials, 20 patients were withdrawn from studies due to abnormalities in liver function tests, including elevations in serum transaminase levels, hyperbilirubinemia, and two patients developed reversible jaundice.

Small decreases in hemoglobin, hematocrit, and neutrophil counts were observed more frequently in patients treated with troglitazone. These decreases were usually not below the normal range and occurred within the first four to eight weeks of therapy. These effects were not associated with any harmful clinical effects and the hemoglobin, hematocrit, and neutrophils typically stabilized and remained within normal limits for up to 2 years of treatment. Troglitazone treatment can result in an increased total plasma volume, which may explain a dilutional effect on these hematological measures.

Studies conducted in rats treated with troglitazone doses ten times the therapeutic human dose resulted in reversible heart enlargement. This effect has not been demonstrated during human clinical trials. Ghazzi evaluated this potential adverse effect in 154 NIDDM patients who were treated with 800 mg of troglitazone or 20 mg - 40 mg of glyburide for 48 weeks. There was no difference in left ventricular mass index from baseline measurements. Subjects treated with troglitazone had significant increases in stroke volume index and cardiac index, as well as, decreases in diastolic blood pressure and estimated total peripheral resistance.

Drug Interactions: Troglitazone may induce the cytochrome P450 3A4 enzyme system causing potentially clinically significant drug interactions with other medications such as astemizole, calcium channel blockers, cisapride, corticosteroids, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, or trimetrexate. Concomitant administration of an oral contraceptive (containing ethinyl estradiol and norethindrone) and troglitazone resulted in a reduction in the plasma concentrations of both agents by approximately 30%. Concurrent use of troglitazone and terfenadine resulted in a decrease in the plasma concentration of terfenadine. The absorption of troglitazone is decreased by approximately 70% when administered with cholestyramine.

Troglitazone does not interact adversely with digoxin, glyburide, warfarin or acetaminophen.

Precautions and Contraindications: Troglitazone therapy is contraindicated in patients with known hypersensitivity to troglitazone or any of the components used in the tablet formulation.

Due to the extensive hepatic metabolism of troglitazone, it should be used with caution in patients with hepatic disease.

Patients who are receiving concomitant therapy of troglitazone with sulfonylurea agents or insulin should be

monitored very closely for hypoglycemia since troglitazone can decrease the requirements for these hypoglycemic agents.

Pharmacokinetic parameters of troglitazone and its major metabolites in elderly patients appear to be comparable to those found in younger patients.

Patients with renal insufficiency do not require dosage adjustments of troglitazone, as clearance of the drug is not related to creatinine clearance.

Dosage and Administration:

Monotherapy: The initial dose is 400 mg once daily taken with a meal. In patients who do not respond to 400 mg daily, the dose may be increased to 600 mg after 6-8 weeks of therapy.

Combination with a sulfonylurea: The initial recommended dose is 200 mg once daily with a meal. Troglitazone dosage may be increased at 2-4 week intervals.

Combination with insulin: The initial recommended dose is 200 mg once daily taken with a meal. The troglitazone dose may be increased to 400 mg daily if there is a lack of a clinical response at the end of 4 weeks of treatment. Insulin dosage should be titrated based on individual response.

The maximum daily dosage of troglitazone is 600 mg.

Table 1. Cost comparison of troglitazone and various oral hypoglycemics

Drug	Usual Dose Range	Cost per month of therapy ($)**
Glyburide*	5 mg - 10 mg in single or divided daily doses	0.55 - 3.40
Glipizide	10 mg - 20 mg in single or divided daily doses	1.08 - 2.03
Metformin*	1500 mg - 2550 mg in divided doses	28.87 - 36.73
Acarbose	50 mg - 100 mg three times daily	28.49 - 36.73
Troglitazone	**400 mg daily**	**100.22**

* NIH CC Formulary Agents
** Federal Supply Schedule

Conclusion: Troglitazone is a novel agent for the treatment of NIDDM that decreases insulin resistance. It appears to be safe and effective as monotherapy and in combination with sulfonylureas or insulin. Troglitazone may prevent the progression to NIDDM in patients with impaired glucose tolerance.

References available upon request.

Editor's Note

We wish to thank Crystal Blankenship, Pharm.D. for her contribution to this issue of Pharmacy Update.

AUGMENTIN: New, Twice-Daily Dosing

Augmentin® (amoxicillin & clavulanic acid), which has traditionally been dosed three times per day, is now available in formulations designed for twice-daily (B.I.D.) dosing. The Inpatient and Outpatient Pharmacies will *only* stock the B.I.D. formulations. Augmentin® dosing is based on the amoxicillin component of the product.

Products on formulary:

875 mg amoxicillin & 125 mg clavulanic acid tablets
500 mg amoxicillin & 125 mg clavulanic acid tablets
400 mg amoxicillin & 57 mg clavulanic acid/5mL oral suspension

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